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Tumor induction in F344/N rats and B6C3F1 mice following inhalation exposure to ethylbenzene

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Abstract

Carcinogenesis studies of ethylbenzene were conducted because of its extensive use as a solvent and because it is structurally similar to the known carcinogen benzene. Groups of 50 male and 50 female Fischer rats and B6C3F1 mice were exposed to ethylbenzene by inhalation at 0, 75, 250, and 750 ppm 6 h per day, 5 days per week, for 2 years. The dose levels were selected based on the results of 13-week studies. In the 750 ppm group of male and female rats, body weights were slightly lower and incidences of renal hyperplasia and tubular neoplasms were significantly increased compared with controls. Incidence of testicular tumors was also significantly increased in male rats. Survival and body weights of the exposed groups of male and female mice and controls were comparable. Incidences of alveolar epithelium metaplasia, alveolar/bronchiolar adenoma, and hepatocyte hypertrophy and necrosis were significantly increased in the 750 ppm male mice and incidences of liver eosinophilic foci and hepatocellular neoplasms were significantly increased in the 750 ppm female mice compared with controls. Ethylbenzene is carcinogenic inducing neoplasms in kidneys and testes in Fischer rats and in lungs in male and liver in female B6C3F1 mice.

Keywords: Carcinogenesis; Ethylbenzene

1. Introduction

Ethylbenzene is naturally present in crude petroleum and is produced commercially by the alkylation of benzene with ethylene. It is used mainly in the manufacture of styrene and cellulose acetate and as an intermediate in the production of diethylbenzene, acetophenone, and ethyl anthraquinone (Federal Register, 1987). Ethylbenzene is a major component (15–20%) of mixed xylenes used as solvents in agricultural and house-

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hold insecticide sprays, rubber and chemical manufacturing industries, household degreasing cleaners, paint, adhesives and rust preventatives (Toftgard and Nilsen, 1982; Fishbein, 1985). Ethylbenzene is also used in motor and aviation fuels as an 'anti-knock' agent (NIOSH, 1979; ILO, 1983).

Ethylbenzene is widely distributed in the environment due to its uses as fuel and as a solvent. It has been detected in ambient air, surface and ground water, human milk, and workers' breath (Lonneman et al., 1968; National Research Council, 1981; Otson et al., 1982; Wallace et al., 1984; STORET, 1986). It has also been found in effluents from wood pulp mills (Nestmann et al., 1980).

Ethylbenzene is readily absorbed from the atmosphere through the lung in humans (Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984) and rats (Chin et al., 1980). Orally administered ethylbenzene is also quickly and effectively absorbed (Climie et al., 1983). Absorption of liquid ethylbenzene through the skin is rapid when compared to similar hydrocarbon compounds such as benzene or styrene (Dutkiewicz and Tyras, 1967).

In humans and in rats, most of the absorbed ethylbenzene is metabolized by the hepatic cytochrome P450 systems to mandelic acid and phenylglyoxylic acid by side-chain oxidation and then excreted in urine (Bardodej and Bardodejova, 1970; Engstrom, 1984; Gromiec and Piotrowski, 1984; Pyykko et al., 1987). Differences in the ethylbenzene metabolic pathways among humans, rats, and rabbits are minor (Chin et al., 1980; Climie et al., 1983). However, in humans, a small amount of phenolic derivatives (4-ethylphenol) is also found (Angerer and Lehnert, 1979; Engstrom, 1984), whereas, in rats, hippuric acid conjugated with glycine is also excreted.

Carcinogenicity studies of ethylbenzene were conducted because of its widespread human exposure and its structural relationship to benzene. The inhalation route of exposure was selected because human exposure to ethylbenzene is mainly by this route.

2. Materials and methods

2.1. Chemical

Ethylbenzene was obtained from ARCO Chemical Company (Newtown Square, PA). Analyses by elemental analyses, Karl Fischer water analysis, iodometric titration for peroxide determination, and gas chromatography indicated that the purity of the compound was greater than 99%. Impurities included 62 ± 3 ppm cumene.

2.2. Exposure system

Ethylbenzene vapor was produced by flash evaporator units and carried from the condensing column into heated stainless-steel transfer lines into Hazleton H-2000 exposure chambers (Lab Products). At the chamber inlets, ethylbenzene vapor was mixed with HEPA- and charcoal-filtered air. Chamber concentrations of ethylbenzene were monitored hourly within the exposure chambers by an on-line gas chromatograph using a flame ionization detector.

2.3. Animals

Groups of 50 male and 50 female F344/N rats and B6C3F1 mice (6 weeks old, obtained from Simonsen Laboratories, Gilroy, CA) were exposed to ethylbenzene by inhalation at 0, 75, 250, or 750 ppm, 6 h plus T90 (15 min) per day, 5 days per week, for 103 (mice) or 104 (rats) weeks. The high dose of 750 ppm, roughly 19% of the 4-h LC50 for rats reported by Smyth et al. (1962), was selected based on 13-week toxicity studies conducted in which no body weight gains, mortality, or histopathological changes were observed (Chan, 1992). The animals were observed twice daily for clinical signs of toxicity. Body weights were recorded weekly for 13 weeks and monthly from week 16 to the end of the study.

2.4. Histopathology

At necropsy, all organs and tissues were examined for grossly visible lesions before being fixed in 10% neutral buffered formalin, trimmed, em-

Table 1
Incidences of kidney lesions in male rats exposed to ethylbenzene for 2 years

	Control	75 ppm	250 ppm	750 ppm
Number examined	50	50	50	50
Single sections (standard evaluation)				
Nephropathy	47 (2.3)[a]	43 (2.4)	47 (2.3)	48 (3.5)**
Renal tubule hyperplasia	2 (3.0)	2 (2.0)	4 (1.3)	12** (1.8)
Adenoma	0	3	2	4*
Carcinoma	0	0	1	3
Adenoma or carcinoma	0	3	3	7**
Step sections (extended evaluation)				
Renal tubule hyperplasia	10	7	9	17**
Adenoma, multiple	0	0	2	4
Adenoma	3	2	7	17**
Carcinoma	0	0	1	3
Adenoma or carcinoma	3	2	8	18**
Single sections and step sections (combined)				
Renal tubule hyperplasia	11 (2.0)[a]	9 (2.3)	11 (2.1)	23** (2.5)
Adenoma, multiple	0	0	2	4
Adenoma	3	5	7	20**
Carcinoma	0	0	1	3
Adenoma or carcinoma	3	5	8	21**

[a] Severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
* $P \leq 0.05$ vs controls by logistic regress (incidence) or by Mann–Whitney U tests (severity).
* $P \leq 0.01$.

bedded in paraffin, sectioned (5–6 μm), and stained with hematoxylin and eosin for microscopic examination.

2.5. Statistical analysis

Differences in survival were analyzed by life table methods (Cox, 1972). Tumor incidence data were analyzed by survival-adjusted methods (Haseman, 1984; NTP, 1996) and by Fisher exact tests and Cochran–Armitage trend tests based on the overall proportion of tumor-bearing animals (Gart et al., 1979). P values reported for tumor comparisons are one-sided.

3. Results

3.1. Rat study

Survival of male rats decreased with increasing dose; the decrease was statistically significant in the 750 ppm group compared with chamber controls. Survival was similar among the female groups. Mean body weights of exposed males and females were slightly (5–10%) lower than those of chamber controls.

3.1.1. Kidney lesions

As shown in Tables 1 and 2, severity of nephropathy and incidences of renal tubule hyperplasia, adenoma or carcinoma were significantly increased in the 750 ppm males and females. Initially, a single section of each kidney was examined microscopically. Because of increased incidences of proliferative lesions in exposed males and a suggestion of a similar effect in females, an additional four sections per kidney were examined from each male and female rat.

Nephropathy in male and female rats was characterized by a spectrum of changes including dilation of renal tubules with hyaline or cellular casts, interstitial fibrosis and mononuclear inflammatory cell infiltration, foci of tubular regeneration, and

Table 2
Incidences of kidney lesions in female rats exposed to ethylbenzene for 2 years

	Control	75 ppm	250 ppm	750 ppm
Number examined	50	50	50	50
Single sections (standard evaluation)				
Nephropathy	38 (1.3)[a]	42 (1 6)*	43 (1.7)**	46 (2.3)**
Renal tubule hyperplasia	0	1 (1.0)	3 (2.3)	3 (1.3)
Adenoma	0	0	0	1
Step sections (extended evaluation)				
Renal tubule hyperplasia	1	1	1	8*
Adenoma	0	0	1	7*
Single sections and step sections (combined)				
Renal tubule hyperplasia	1 (1.0)	2 (1.0)	4 (2.2)	10** (1 8)
Adenoma	0	0	1	8**

[a] Severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
* $P \leq 0.05$ vs controls by logistic regression (incidence) or by Mann–Whitney U tests (severity).
** $P \leq 0.01$.

transitional epithelial hyperplasia of renal papilla. Renal tubule hyperplasia, adenoma, and carcinoma constitute a morphologic and biologic continuum. Hyperplasia was a focal lesion consisting of tubules which were enlarged up to two to three times the diameter of a normal tubule and which were lined by increased numbers of epithelial cells that partially or totally filled the tubule lumen. Hyperplasia was considered a preneoplastic lesion and was distinguished from regenerative epithelial changes commonly seen as a component of chronic nephropathy. Renal tubule adenomas were discrete proliferative lesions, which were larger than focal hyperplasia and which tended to form more complex, usually multilobulated structures. Carcinomas were macroscopic tumors which projected beyond the capsular surface. Microscopically, carcinomas were characterized by more pleomorphic cells, more prominent vascular supply, and large central areas of necrosis.

3.1.2. Testicular lesions

In the 750 ppm males, incidence of interstitial cell adenoma was significantly greater than that in the chamber control group; incidence of bilateral testicular adenoma was also significantly increased; whereas incidence of interstitial cell hyperplasia in 750 ppm males was significantly decreased (Table 3). Interstitial cell adenoma is a common neoplasm in male F344/N rats and is composed of nodular aggregates of large polyhedral cells with foamy or eosinophilic cytoplasm which extend between seminiferous tubules and cause compression of the surrounding tubules. This neoplasm will develop in nearly all F344/N rats if allowed to complete their natural life span; however, ethylbenzene appeared to enhance its development (Table 4).

3.2. Mouse study

Survival and body weights of exposed groups of male and female mice were similar to that of chamber controls.

3.2.1. Lung lesions

Incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in males increased with a positive trend and in the 750 ppm males were significantly greater than those in the chamber control group (Table 5). No differences were observed in incidence rates of alveolar/bronchiolar adenomas and/or carcinomas among the female groups. Alveolar/bronchiolar neoplasms were nodular proliferations within the lung parenchyma which caused variable compression depending on size.

Table 3
Incidences of testicular lesions in male rats exposed to ethylbenzene for 2 years

	Control	75 ppm	250 ppm	750 ppm
Number examined	50	50	50	50
Interstitial cell				
Hyperplasia	14 (1.5)	19 (1.2)	12 (1.3)	8* (1.1)
Adenoma	36	33	40	44**
Bilateral adenoma	27	23	32	40**

* $P \leq 0.05$ vs controls (logistic regression test).
** $P \leq 0.01$.

Adenomas were typically well circumscribed nodules composed of monomorphic cuboidal cells arranged in solid or papillary patterns. In carcinomas the borders were less distinct and the neoplastic cells were cuboidal to columnar in shape and exhibited greater cytologic atypia. Proliferative change in the lung diagnosed as alveolar epithelial metaplasia was observed in exposed males and females; the incidence was significantly increased in the 750 ppm males. Metaplasia was characterized by the presence of cells morphologically similar to bronchiolar epithelial cells lining the alveolar spaces adjacent to terminal bronchioles.

3.2.2. Liver lesions

Incidence of hepatocellular adenoma and adenoma or carcinoma (combined) in females occurred with a positive trend; the incidence was significantly greater in the 750 ppm group than those in the chamber controls (Table 6). Multiple adenomas were found in all exposed groups of females, and multiple carcinomas were found in two 750 ppm females, but multiple liver neoplasms were not found in control females. Hepatocellular adenomas consisted of nodules of hepatocytes which compressed adjacent liver parenchyma and lacked the normal lobular and sinusoidal pattern. Hepatocellular carcinomas were large masses composed of anaplastic hepatocytes forming solid sheets or trabecular patterns.

Table 4
Incidences of testicular adenoma at varying time periods for male rats exposed to ethylbenzene for 2 years

Survival (days)	0 ppm	750 ppm
<400	0% (0/2)	0% (0/3)
400–600	33% (3/9)	92% (22/24)
600-Sacrifice	67% (18/24)	95% (20/21)
Terminal sacrifice	100% (15/15)	100% (2/2)
Total	72% (36/50)	88% (44/50)

In addition to liver neoplasms, the incidence of eosinophilic foci in the liver was significantly greater in the 750 ppm females than in he controls. This lesion, composed of focal collections of cells which have altered staining characteristics which blend into surrounding hepatic cords with little or no compression, is considered to be a precursor to hepatocellular neoplasia.

A spectrum of nonneoplastic liver changes related to ethylbenzene exposure in male mice included syncytial alteration of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis were observed. Syncytial alteration was seen in all male exposed groups with concentration-dependent increases in incidence. This change consisted of the presence of greatly enlarged hepatocytes containing multiple nuclei, generally five or more, either randomly scattered throughout the liver lobule or with a tendency to cluster in centrilobular areas. Hypertrophy of hepatocytes occurred in the centrilobular zones of 750 ppm males and was characterized by cells with increased amounts of cytoplasm and enlarged nuclei. Syncytial alteration and hypertrophy frequently occurred in the same animal.

Table 5
Incidences of lung lesions in mice exposed to ethylbenzene for 2 years

	Control	75 ppm	250 ppm	750 ppm
Male				
Number examined	50	50	50	50
Alveolar epithelium				
Hyperplasia	1 (1.0)	5 (2.6)	2 (1.5)	4 (2.0)
Metaplasia	0	1 (1.0)	2 (1.0)	6* (1.2)
Alveolar/bronchiolar				
Adenoma	5	9	10	16**
Carcinoma	2	1	5	3
Adenoma or Carcinoma	7	10	15	19**
Female				
Number examined	50	50	49	50
Alveolar epithelium				
Hyperplasia	0	1 (2.0)	3 (2.0)	1 (3.0)
Metaplasia	0	0	0	1 (2.0)
Alveolar/bronchiolar				
Adenoma	4	4	5	8
Carcinoma	0	2	0	0
Adenoma or carcinoma	4	6	5	8

* $P \leq 0.05$ vs controls (logistic regression test).
** $P \leq 0.01$.

Hepatocellular necrosis was evident as random single cell necrosis, generally of hypertrophied cells.

3.2.3. Thyroid lesions

Increased incidence of thyroid follicular cell hyperplasia was observed in the exposed males (control: 21/50; 75 ppm: 21/50; 250 ppm: 29/50; 750 ppm: 32/50) and females (18/50, 23/50, 25/50, 35/50). Thyroid hyperplasia was typically a focal noncompressive proliferation with simple papillary infoldings of follicular epithelial eells. There were no corresponding increases in the incidence of adenomas of the thyroid gland.

3.2.4. Pituitary gland lesions

Incidences of hyperplasia of the pituitary gland pars distalis was significantly increased in the 250 and 750 ppm females relative to controls (10/48, 12/49, 23/47, 22/49). The lesions were seen as focal, poorly delineated, monomorphic increases of cells which had no compressive features or altered arrangement.

4. Discussion

In the standard histopathologic evaluation of the kidney in the present study, the incidence of renal tubule adenoma in the 750 ppm male rats was significantly greater than that in the chamber controls. Step sections evaluation of the kidneys identified many more adenomas and a few additional carcinomas. In addition, multiple renal tubule adenomas were found in the 250 and 750 ppm males. The standard evaluation and step sections evaluation (combined) showed significantly increased incidences of renal tubule adenoma, renal tubule adenoma or carcinoma (combined), and renal tubule hyperplasia in the 750 ppm male rats as well as positive trends across the exposure groups. In the standard evaluation of female rat kidneys, no significant increases in incidences of renal lesions were observed. In the step sections evaluation, the incidences of renal tubule hyperplasia and renal tubule adenoma were significantly increased in the

Table 6
Incidences of liver lesions in mice exposed to ethylbenzene for 2 years

	Control	75 ppm	250 ppm	750 ppm
Male				
Number examined	50	50	50	50
Hepatocyte				
Hypertrophy	1 (1.0)	0	0	17** (1.1)
Necrosis	1 (1.0)	1 (2.0)	3 (1.3)	10** (1.8)
Syncytial alteration	0	5 (1.0)	8**(1.4)	23** (1.1)
Female				
Number examined	50	50	50	50
Eosinophilic focus	5 (1.8)	7 (1.4)	6 (1.5)	22** (2.0)
Hepatocellular				
Adenoma, multiple	0	1	3	4
Adenoma	6	9	12	16*
Carcinoma, multiple	0	0	0	2
Carcinoma	7	4	3	12
Adenoma or carcinoma	13	12	15	25*

* $P \leq 0.05$.
** $P \leq 0.01$.

750 ppm females compared with the chamber controls.

Kurokawa et al. (1983) first reported that a greater incidence of rat kidney lesions was found when multiple kidney sections were examined compared with single sections. This was expected considering the very small size of many of the tubule cell adenomas typically seen in the kidney. The NTP has compared lesions from single and multiple kidney sections and found increased incidences of renal tubule hyperplasia and renal tubule adenoma in multiple sections from male rats (Eustis et al., 1994), agreeing with the findings of Kurokawa et al. (1983). However, few additional neoplasms were identified in female rats or in male or female mice (Eustis et al., 1994). In the present studies, additional incidences of renal tubule hyperplasia and renal tubule adenoma were found in step sections from male and female rats.

Nephropathy is commonly found in aging male and, to a lesser degree, female rats. In the step sections evaluation of the kidneys the severity of nephropathy and incidences of renal tubule hyperplasia in the 750 ppm males and females were increased. Ethylbenzene may have exacerbated the age-related nephropathy development in rats or exerted toxic injury to the renal cells and induced compensatory cell replication of the renal tubule epithelium. Whether it was a direct effect of ethylbenzene or an indirect result of elthylbenzene induced cytotoxicity, the renal tubule lesions in male and female rats were considered exposure related. Male rats appeared to be more sensitive to the renal toxic effect of ethylbenzene than female rats, and that may account for the early deaths in the 750 ppm males.

Following exposure to certain hydrocarbons, male rats develop renal tubule hyaline droplets, attributed to accumulation of α2u-globulin in the kidney. The accumulation of α2u-globulin is known to lead to nephropathy and renal tubule neoplasm development in male rats. This spectrum of non-neoplastic changes differs from the chronic progressive nephropathy commonly found in aging male rats (USEPA, 1991). No clear evidence of hyaline droplets was seen in the kidneys of male F344/N rats exposed to ethylbenzene for 13 weeks (Chan, 1992) or 2 years (present studies), and, thus, this proposed mechanism did

not appear to contribute to the proliferative renal tubule lesions in male or female F344/N rats in the studies reported here.

After a 6-h inhalation exposure to ethylbenzene in male Wistar rats, the major metabolites identified in urine were α-methylbenzyl alcohol (1-phenylethanol), mandelic acid, phenylglyoxylic acid, phenylacetic acid, and benzoic acid. Minor metabolites included ω-hydroxyacetophenone, 1-phenyl-1,2-ethanediol, acetophenone, *p*-hydroxyacetophenone, and phenylglyoxal (Engstrom, 1984). Blood metabolises of ethylbenzene were difficult to identify and measure (Engstrom, 1984). α-Methylbenzyl alcohol was negative for mutagenicity (NTP, 1990) and did not induce sister chromatic exchanges in cultured human lymphocytes (Norppa and Vainio, 1983). However, α-methylbenzyl alcohol has been shown to enhance nephropathy and induce renal tubule cell adenoma or adenocarcinoma in male F344/N rats (NTP, 1990), but had no effect on nephropathy and renal tubule cell lesions in female F344/N rats. The kidney toxicity and carcinogenicity observed in both male and female rats in the present studies suggested that ethylbenzene is more potent than α-methylbenzyl alcohol in causing renal toxicity. Other metabolites, such as an epoxide or diolepoxide after ring oxidation (Engstrom, 1984), phenylglyoxal bearing a reactive aldehyde group, or those postulated in benzene metabolism such as hydroquinone, benzoquinone (Snyder and Hedli, 1996), and benzene diolepoxide-2 (Busby et al., 1990) may contribute to the renal toxicity and carcinogenicity of ethylbenzene. Further studies to identify the active species are needed. It should be noted that ethylbenzene is not mutagenic or clastogenic (NTP, 1996).

The increased incidence of testicular adenoma observed in male rats in the 750 ppm group was considered related to ethylbenzene exposure. This is evidenced by the finding that 92% (22/24) of the 750 ppm male rats that died between day 400 and day 600 had testicular adenoma, whereas only 33% (3/9) of the controls that died early had testicular adenoma (Table 4). The incidence of bilateral adenoma was also increased in 750 ppm males. Testicular adenoma develops in nearly all rats in the latter part of their life, but in inhalation studies, the incidence is low compared with feeding and gavage studies (Haseman et al., 1997). Ethylbenzene appeared to hasten the development of testicular adenomas. How ethylbenzene accomplishes this effect is not clear. There were no testicular effects detected in the 13-week studies (Chan, 1992). α-Methylbenzyl alcohol may not be involved since it inhibits testicular adenoma (NTP, 1990).

Structurally, ethylbenzene is related to benzene. Benzene is a multipotential carcinogen suppressing bone marrow cellularity and inducing leukopenia, leukemia, and neoplasms in Zymbal gland, oral cavity, and skin in rats and Zymbal gland, lymph gland, lung, Harderian gland, preputial gland, mammary gland, ovary, forestomach, and liver in mice after gavage dosing (NTP, 1986). Benzene is metabolized to benzene oxide, benzene oxepin, benzene dihydrodiol, phenol, hydroquinone, trihydroxybenzene (benzenetriol), catechol, benzoquinone, and *trans*,*trans*-muconaldehyde (Sabourin et al., 1989, 1992; Snyder and Hedli, 1996). The metabolites proposed for the hematotoxicity are hydroquinone, benzoquinone, catechol, and benzenetriol (Snyder and Hedli, 1996) and for lung tumors in mice are benzene oxide, benzene dihydrodiol, and benzene diolepoxide-2 (Busby et al., 1990). Although benzene and ethylbenzene are structurally related the metabolites, target organs, and mechanism of action of benzene appear quite different from that of ethylbenzene.

In the mouse studies, the incidences of alveolar epithelial metaplasia and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly increased in 750 ppm male mice, but not in 750 ppm female mice. The difference in response between males and females to ethylbenzene is not clear and is probably not related to air volume inhaled.

Increased incidences of hepatocellular adenoma or carcinoma (combined) and liver eosinophilic foci were observed in the 750 ppm groups of female mice but not in male mice in the present studies. A significant increase in absolute liver weight was observed in male and female mice exposed to ethylbenzene at 750 ppm and higher in the NTP 13-week studies (Chan, 1992). Increased

absolute and relative liver weights were also reported in female B6C3F1 mice exposed to ethylbenzene by inhalation (Cragg et al., 1989). The female mouse liver appears to be more sensitive to the effects of ethylbenzene than the male mouse liver; however, the relationship between increased liver weight and liver neoplasm incidence in the female mice is not clear.

It is also not clear why male and female B6C3F1 mice had different neoplasm responses to ethylbenzene exposure. There is little data available on which to judge why ethylbenzene affected male and female endocrine systems differently, although an exposure-related increase in incidence of pituitary gland (pars distalis) hyperplasia was seen in female mice. Ethylbenzene induced an exposure-related increase in incidence of hyperplasia in thyroid gland of male and female mice, but there was no difference between males and females in incidence observed.

Phenylglyoxylic and mandelic acids were effective in causing brain dopamine depletion in vitro (Mutti and Franchini, 1987) and in vivo (Mutti et al., 1988). On the other hand, Andersson et al. (1981) reported that male Spraque–Dawley rats exposed to ethylbenzene by inhalation at 2000 ppm, 6 h per day for 3 days, had increases in dopamine and noradrenaline levels in the hypothalamus and the median eminence. Such neurotoxic effects would disturb brain function and cause neurobehavioral and neuroendocrine changes and may be related to the sex difference in response to ethylbenzene exposure.

The sex and species differences and organ specificity in the carcinogenic effects of ethylbenzene are unexpected findings. The mechanisms of action of ethylbenzene carcinogenesis in rats and mice remain to be defined.

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